Low-dose radioiodine given six-monthly in Graves' disease[1]

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Summary: Experience using low-dose radioiodine given six-monthly instead of yearly in hyperthyroid patients with Graves' disease is reported. One hundred and thirty-five patients have been treated over a three-year period with 74 MBq (2 mCi) doses of ^{131}I. Thirty-eight percent were controlled with a single dose. Those patients requiring more than one dose were treated with a further 74 MBq (2 mCi) ^{131}I at six-monthly intervals until euthyroid. Using this approach, 46% were euthyroid one year after starting treatment, and 75% were euthyroid at two years. The incidence of hypothyroidism following treatment was 2.2% at one year, with a yearly incidence thereafter of 4–6%. Six-monthly scheduling of low-dose radioiodine in Graves' disease can reduce the time taken to become euthyroid, compared with conventional yearly low-dose treatments. Further follow up is required to confirm the present low incidence of hypothyroidism following treatment.

Introduction

The use of radioiodine is well established as a safe and effective treatment for hyperthyroidism (Halnan 1983). Whilst several large series have analysed the number of euthyroid and hypothyroid patients after radioiodine treatment, there is little published data on the time taken for patients to become euthyroid with this method of treatment. The use of low-dose regimens reduces the incidence of hypothyroidism following treatment (Goolden & Russell Fraser 1969, Smith & Wilson 1967) but many patients require more than one dose of radioiodine to become euthyroid. Conventionally, repeated doses of radioiodine are given, when necessary, at yearly intervals. This results in a considerable delay in achieving control, particularly for the 20–30% of patients who require three or more doses when low-dose regimens are used.

Between 1972 and 1978, hyperthyroid patients with Graves' disease were treated at this hospital using 2 mCi ^{131}I, repeated yearly as required (Lowdell *et al.* 1985). From January 1979 the treatment policy in the Royal Marsden Hospital Thyroid Clinic was modified so that patients remaining hyperthyroid after their first dose of ^{131}I were given repeated doses as necessary every six months until euthyroid. The results of the first three years of this new policy of frequent low-dose radioiodine administration have now been analysed with, in addition to the usual parameters of thyroid function, particular attention to the time taken for patients to become euthyroid.

Method

The patients reported here were referred to the Royal Marsden Hospital Thyroid Clinic between January 1979 and December 1981.

Low-dose treatment using 74 MBq (2 mCi) of ^{131}I is selected for hyperthyroid patients with Graves' disease. Patients with multinodular goitre, solitary hot nodules and those with cardiac symptoms (cardiotoxic) are given a larger dose of 370 MBq (10 mCi) of ^{131}I. The diagnosis of Graves' disease is based on a positive family history, clinical signs (eye signs, clubbing, vitiligo,

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Table 1. Patient characteristics related to number of doses of radioiodine received

Doses received	No. of patients	Mean age	Female:male ratio	Mean time (years) from original diagnosis	Mean follow up (years)
1	51 (38%)	64	3:1	4.4	3.6
2	44 (32%)	57	7:1	3.6	3.4
3	20 (15%)	63	7:1	6.0	4.0
4	13 (10%)	60	10:1	4.2	3.7
5	7 (5%)	60	6:1	8.0	3.5
All patients	135 (100%)	61●	6:1	4.5	3.6

● Eight patients were aged less than 40 years

etc), thyroid function tests and positive autoantibodies, together with subsequent diffuse uptake on thyroid isotope scanning.

Having been assessed in the clinic initially and selected for low-dose ^{131}I treatment, patients have their anti-thyroid medication stopped 3–4 days prior to administration of iodine. No attempt is made to measure the size of the gland as a standard dose of 74 MBq (2 mCi) is given to all patients; this is administered orally on an outpatient basis in the Nuclear Medicine Department. The following day thyroid scanning is performed and 24-hour ^{131}I uptake is measured. In those with severe hyperthyroidism, antithyroid medication is resumed three days following this procedure, but in less severe cases no further antithyroid medication is given. Patients requiring β-blockers for control of symptoms remain on these throughout.

Patients are then seen at six weeks after administration of radioiodine and subsequently every 2–3 months. Where appropriate, antithyroid medication is gradually withdrawn. Thyroid function tests (T4, T3 and TSH) are repeated prior to each visit so that results of recent tests are available when patients are seen in the clinic. Patients remaining hyperthyroid after six months are given a further dose of 74 MBq (2 mCi) ^{131}I. Patients are designated euthyroid when they remain clinically and biochemically euthyroid, having discontinued all antithyroid medication.

Results

Between January 1979 and December 1981, 140 patients were selected for initial treatment with 74 MBq (2 mCi) ^{131}I. Five died within a few months of treatment with radioiodine without documentation of their thyroid status, the causes of death being alcoholic cirrhosis (1), carcinoma of the breast (1), ischaemic heart disease (2), and pneumonia and renal failure (1). This report concerns the remaining 135 patients.

Eighteen patients who remained thyrotoxic after initial treatment with 74 MBq (2 mCi) ^{131}I subsequently received 370 MBq (10 mCi) doses. This was on the basis of a multinodular goitre on thyroid scanning after their initial therapy dose of radioiodine. All other patients received repeated doses of 74 MBq (2 mCi) ^{131}I, as described above.

Patients have been followed up for a mean period of 3.6 years. Only 9 patients remain thyrotoxic (2 have had two doses ^{131}I, 3 have had three doses, and 4 have had five doses). In addition, 3 patients became directly hypothyroid after their final dose of ^{131}I. The general characteristics of the population are shown in Table 1.

Fifty-one patients (38%) required only a single dose of radioiodine. The only striking difference between this group and those requiring more than one dose was the low female:male ratio. Of the 135 patients, 13 (54%) of the 24 males compared with 38 (34%) of the 111 females required only a single dose. The relationship between age, time from diagnosis, previous treatment and antibody status is shown in Table 2. There appears to be no relationship between these parameters and number of doses of radioiodine required. Previous medical treatment in

Table 2. Previous treatment and antibody status

Doses ^{131}I received	Previous treatment ($n=135$)		Positive antibody status ($n=98$)●	
	Medical	Surgical	Microsomal	Thyroglobulin
1	37 (72%)	5 (10%)	15 (47%)	4 (12·5%)
2	32 (73%)	5 (11%)	18 (53%)	11 (31%)
3	14 (70%)	5 (25%)	10 (59%)	4 (23%)
4	13 (100%)	1 (8%)	5 (55%)	0
5	5 (71%)	0	4 (80%)	1
All patients	101 (75%)	16 (12%)	52 (53%)	20 (20%)

●A total of 98 patients had antibody status determined

Table 3. Time to become euthyroid and relation to number of doses of ^{131}I received

	All patients	No. of doses ^{131}I received				
		1	2	3	4	5
Mean time (months) to become euthyroid:						
From referral	13	5.1	13.1	24.3	28.6	31.3
From final dose of ^{131}I	4.7	5.1	5.0	4.0	4.4	3.25

these patients was carbimazole for varying lengths of time with relapse on withdrawal, and in 3 cases propylthiouracil was used because of intolerance to carbimazole. Surgery in all cases had been partial thyroidectomy. Twelve of the 16 patients treated surgically also had medical treatment prior to referral. Thirty (22%) patients had had no previous treatment, being referred for ^{131}I as their primary treatment. The high proportion of patients requiring three doses having had previous surgery, and of those requiring four doses having had previous medical treatment, is probably related to the small numbers of patients in these groups.

The principal aim of this study was to assess the time taken to achieve control. As expected, the time from first referral to the Thyroid Clinic to becoming euthyroid increased with the number of doses required (Table 3). It is of interest that the time taken to become euthyroid following the final dose of radioiodine was remarkably constant. It can be seen from Figure 1 that 46% of patients were euthyroid after one year and 75% after two years. The characteristics of the 22 patients who became hypothyroid are compared with those of the total patient population in Table 4, and Tables 5 and 6 show the time taken to become hypothyroid and its relation to the number of doses of radioiodine given. The one-year incidence of hypothyroidism appeared to be very low and after that a yearly incidence of 4–6% was seen. There is no relationship between number of doses given and incidence of hypothyroidism. Of the 10 patients who developed hypothyroidism within six months of their final dose of ^{131}I, 2 had received a single dose, 3 had received two doses, 4 had received three doses and one had received four doses.

Discussion

The use of radioiodine in Graves' disease has been advocated as the treatment of choice for the majority of adults (Becker 1984), having definite advantages over the alternatives of surgery or antithyroid medication.

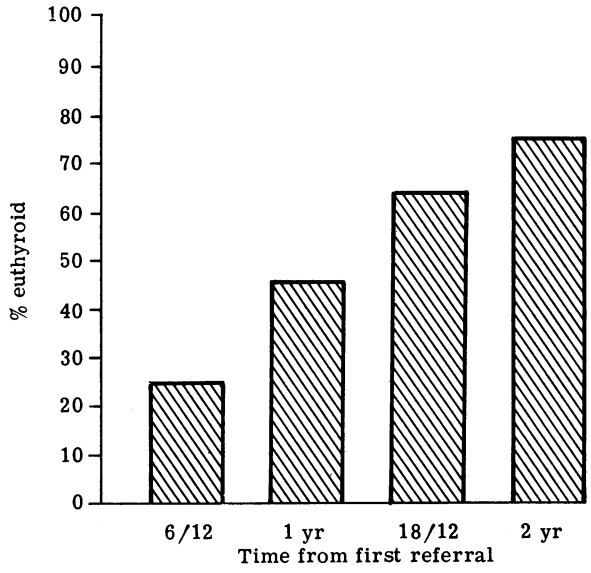

Figure 1. Rate of control. Of 135 patients, 33 (24%) were euthyroid at 6 months, 62 (46%) at 1 year, 85 (63%) at 18 months, and 101 (75%) at 2 years

The adoption of low-dose ^{131}I has reduced the incidence of hypothyroidism following this procedure. However, this continues to be a problem, with a cumulative incidence in the present series of 4–6% per year, and one recent large series reported an incidence after one year of 12%, with a cumulative incidence of 76% at 11 years (Srimada *et al.* 1984). This cumulative effect is explained by radiation damage to DNA causing progressive loss of cells as they are stimulated to divide (Al-Himadi & Wilson 1965). However, the natural history of untreated Graves' disease shows a variable incidence of hypothyroidism and this should also be considered in interpreting the results of any treatment (Irvine *et al.* 1977).

The main disadvantage of low-dose treatment lies in the delay in patients becoming euthyroid, with around half of all patients requiring a second dose of radioiodine and up to a third requiring three or more doses. In this study it was hoped that by giving subsequent doses

Table 4. Characteristics of hypothyroid patients compared with all patients

	Hypothyroid patients ($n=22$)	All patients ($n=135$)
Mean age (range)	57.8 (26–71)	61 (26–89)
Female:male	4.5:1	6:1
Mean time (years) from diagnosis	2.6	4.5
No. (%) previous medical treatment	17 (77%)	101 (75%)
No. (%) previous surgical treatment	3 (14%)	16 (12%)
No. (%) no previous treatment	5 (23%)	30 (22%)
No. (%) positive microsomal ABs titre > 1/400●	10 (62.5%)	52 (53%)
No. (%) positive thyroglobulin ABs titre > 1/20●	0	20 (20%)

●98 patients in all, and 16 of 22 hypothyroid patients, had ABs measured

Table 5. Incidence of hypothyroidism related to number of doses ^{131}I received

Doses received	Number (%) hypothyroid
1	6 (12%)
2	8 (18%)
3	4 (20%)
4	3 (23%)
5	1 (14%)
	22 (16%)

Table 6. Time taken to become hypothyroid

Period during which hypothyroidism developed	No. (%) of patients becoming hypothyroid: Time from referral	Time from final ^{131}I
<6 mo	3 (2.2%)	10 (7%)
7 mo–1 yr		4 (3%)
13 mo–2 yr	8 (5.9%)	3 (2.5%)
25 mo–3 yr	6 (4.4%)	3 (2.5%)
37 mo–4 yrs	5 (4.2%)	2 (1.7%)
Total	22 (16%)	22 (16%)

where required at six-monthly rather than yearly intervals, the delay in achieving normal thyroid function might be reduced.

The patients in this study were comparable with those reported elsewhere in terms of age, sex ratio, antibody status and previous treatment, and after treatment a similar incidence of hypothyroidism was seen. The difference of note seen in this study was the preponderance of males requiring only a single dose of radioiodine for control.

The incidence of hypothyroidism in the first year appears particularly low and some workers have suggested that pretreatment with antithyroid drugs may reduce the incidence of early hypothyroidism (Aro *et al.* 1981, Connell *et al.* 1984). One of the 3 patients who became hypothyroid in the first year had had no previous treatment; the other 2 had received carbimazole for six and seven months respectively. Over the four years there was no evidence that previous treatment influenced the incidence of hypothyroidism.

In this study 46% of patients had become euthyroid at one year from initial treatment with radioiodine, rising to 75% at two years. These periods are perhaps slightly longer than might theoretically be expected from six-monthly scheduling of radioiodine, but this may be explained by the fact that some patients require more than six months to have their carbimazole tailed off when seen every 2–3 months in the clinic. Because of this, whilst most patients who require subsequent doses of radioiodine do so within six months, some will have longer periods between doses, being controlled on a small reducing dose of carbimazole but relapsing some time after stopping medication completely.

The finding that there appears to be a consistent period of 4–5 months (mean 4.7 months) after the final dose of ^{131}I for a patient to become euthyroid is of some interest, and suggests that six-monthly intervals between doses is optimum and any further reduction is inappropriate, increasing the risk of treating patients who have already had sufficient ^{131}I to become euthyroid.

An alternative approach in treating Graves' disease with radioiodine is to give a large ablative dose with the intention of inducing hypothyroidism, which is then treated with appropriate thyroxine replacement. One recent study found that after a single dose of 555 MBq (15 mCi), 64% of patients became hypothyroid within the first year and a further 27% became euthyroid (Kendall-Taylor *et al.* 1984). Thus, most patients can have their hyperthyroidism controlled within the first year by this approach – but the price of this is lifelong thyroxine replacement. In the present study, in which frequent small doses of radioiodine were used, 46% of patients were euthyroid at one year (and only 2.2% hypothyroid), and at two years 75% were euthyroid with 8% hypothyroid. It is clearly preferable to restore patients to the euthyroid state if at all possible, so that the majority of patients need no further medication.

The incidence of hypothyroidism in these patients is at present 4–6% per year, in keeping with other low-dose series, but clearly this needs to be interpreted with caution since a continuing incidence of hypothyroidism is to be expected and careful follow up of these patients with regular thyroid function tests remains essential.

In conclusion, therefore, this approach retains the advantages of low-dose radioiodine whilst overcoming the major disadvantage – that is, the time taken to achieve control. Longer follow up will reveal whether the present low incidence of hypothyroidism persists. There is probably no ideal dose schedule for radioiodine, since rapid control of hyperthyroidism and low incidence of hypothyroidism are mutually exclusive. There are clear indications for high-dose ^{131}I treatment (Hamberger & Sukhannery 1968): where there are cardiac symptoms (Scott *et al.* 1984), a multinodular goitre or a single toxic nodule. In Graves' disease without cardiac complications, where radioiodine is now considered the treatment of choice, six-monthly low-dose ^{131}I may provide more rapid control than other low-dose regimens, with a lower incidence of hypothyroidism than with larger doses of radioiodine.

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